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Clinical tumour sequencing for precision oncology: time for a universal strategy

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Abstract

Routine, comprehensive molecular characterization of patient tumours has the potential to accelerate therapeutic advances and inform cancer biology. Here, we describe insights from the implementation of an enterprise-wide, prospective clinical sequencing strategy at an academic cancer centre.

Tumour genomic profiling of a limited number of cancer-associated genes to direct therapeutic management is established as standard care in melanoma and non-small-cell lung, breast, ovarian and colorectal cancers. The utility of broader tumour molecular profiling and its role in other cancer types remain areas of active debate and controversy. The recent US Food and Drug Administration (FDA) approval of the programmed cell death protein 1 (PD1) inhibitor pembrolizumab for the treatment of solid tumours, which are microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) — the first approval of a cancer therapy for a specific genomic feature independent of tissue site of origin — will substantially influence this debate. As we expect next-generation sequencing (NGS) to prove to be the most efficient method to characterize MSI-H or dMMR status, we believe that the need to guide standard-of-care use of immune checkpoint blockade will prompt the rapid adoption of NGS-based tumour profiling in an increasing number of cancer types. Here, we review our experience with the implementation of a universal NGS-based tumour molecular profiling initiative at our academic cancer centre, Memorial Sloan Kettering Cancer Center (MSKCC), and advocate for comprehensive genomic characterization of all patients with solid tumours who require systemic treatment.

Prompted by insights from the retrospective analysis of exceptional responders and the increasing availability of highly selective targeted therapies, our centre began offering

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Competing interests

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comprehensive clinical tumour genomic profiling to all patients with metastatic cancer in 2014. Tumours are analysed using MSK-IMPACT (integrated mutation profiling of actionable cancer targets), a hybridization capture-based NGS assay designed to identify mutations, copy number alterations and select gene fusions in several hundred cancer-associated genes. An important aspect of our strategy was the concurrent analysis of tumour and matched normal DNA to enhance the accuracy of somatic mutation calling and to facilitate the identification of pathogenic germline mutations associated with increased heritable cancer risk or drug sensitivity. To accelerate the discovery of novel predictive and prognostic biomarkers, patients were also asked to consent to future research use of remaining DNA or tumour tissue for analysis with more extensive profiling methods such as whole exome, genome or transcriptome sequencing. Importantly, MSK-IMPACT testing was performed in a Clinical Laboratory Improvement Amendments (CLIA)-compliant clinical laboratory, with results reported in the electronic medical record from which they could be acted upon by treating physicians. Automated systems were also created to facilitate matching of patients to molecularly appropriate clinical trials.

We recently published findings from the first 10,000 patients sequenced by MSK-IMPACT[1]. This analysis delineated the molecular landscape of metastatic cancer in a heavily pretreated real-world cohort. 37% of patients harboured at least one therapeutically actionable alteration and 11% were matched to genome-directed clinical trials at our centre. In patients with lung adenocarcinoma, a cancer subtype in which tumour molecular profiling is needed to guide the selection of standard therapies, 37% of patients received a genotype-matched standard or investigational drug, with the use of matched therapy strongly influenced by the level of pre-existent clinical evidence that the mutation identified predicts the drug response[2]. Additionally, 55% of pathogenic or likely pathogenic germline mutations identified by MSK-IMPACT would not have been detected using current clinical guidelines[3].

Critics of routine molecular profiling often highlight the low proportion of patients in which a matched investigational therapy is administered and the modest level of evidence that such investigational therapies result in patient benefit. These valid concerns underscore that the clinical trial portfolios of even the largest cancer centres cannot possibly include all potential matched therapies, and that eligibility criteria related to coexisting medical issues may also preclude trial enrolment. We acknowledge that the proportion of patients for whom genomic profiling will elucidate currently targetable alterations varies among cancer types, and is relatively low in certain disease groups. However, the emergence of a growing number of tissue type-agnostic targets, including MSI-H or dMMR status and tropomyosin receptor kinase (TRK) fusions, promise to shift the debate in support of universal tumour profiling in all patients for whom disease-specific standard therapies are unlikely to result in disease cure. Treatment with immune checkpoint blockade[4] and TRK inhibitors[5] in the appropriate genomic populations can result in dramatic and durable responses, and a more limited subset of patients to test for these alterations cannot be determined a priori. Given cost considerations and the often-limited quantity of tumour material available for testing in many cancer patients, only a minority of the rapidly increasing number of predictive biomarkers of potential interest can be assessed using standalone companion diagnostics or traditional assays such as immunohistochemistry. NGS-based tumour profiling thus

represents the only practical method to assess for the presence of the numerous standard and investigational biomarkers of potential interest in an individual patient.

In our experience, simultaneously screening for multiple genome-selected clinical trials using MSK-IMPACT was crucial in facilitating enrolment to and completion of clinical trials of novel genome-directed therapies. For example, the majority of patients enrolled in each of the recent multicentre basket trials of the TRK inhibitor larotrectinib[5], the AKT inhibitor AZD5363 (REF.[6]) and the HER kinase inhibitor neratinib[7] were identified by NGS-based profiling assays, such as MSK-IMPACT. Thus, broader tumour genomic profiling allows for promising hypotheses to be more rapidly tested in patients, with both positive and negative outcomes then used to guide the future development of novel therapies. Importantly, the value of genomic sequencing extends far beyond the direct clinical benefit it provides to individual patients. We recognized early on that by providing real-time access to genomic data and accompanying clinical annotation to all researchers at our institution, we could accelerate translational research programmes at MSKCC and beyond. Novel, and in many cases unexpected, somatic and germline variants identified by MSK-IMPACT have prompted numerous translational and basic science research initiatives directed at understanding the function and potential therapeutic importance of these variants. Guided by this early success, this data sharing effort is now being extended through multi-institutional collaborations such as the American Association for Cancer Research (AACR) Project Genomics Evidence Neoplasia Information Exchange (GENIE).

The recent FDA authorization of MSK-IMPACT and FoundationOne CDx (a commercial NGS panel) represent a critical inflection point in precision oncology. We believe that the current data support prospective, comprehensive tumour characterization in all patients with metastatic solid tumours to identify both cancer type-specific predictive biomarkers of drug response, such as anaplastic lymphoma kinase (ALK) fusions in non-small-cell lung cancer, and pan-cancer biomarkers, such as MSI-H or dMMR status. We further believe that the profiling platform used to identify standard-of-care biomarkers can provide additional value by identifying investigational biomarkers of response and resistance to standard and investigational drugs, as well as by contributing to more accurate disease sub-classification and prognostic assessment. While recognizing privacy and cost considerations, we also believe that NGS platforms should incorporate the analysis of matched normal DNA to permit more accurate classification of somatic variants, enable the identification of mutations associated with clonal haematopoiesis[8] and provide insight into heritable cancer risk.

We acknowledge that simply increasing the adoption of NGS-based tumour profiling alone will be insufficient to address the unmet needs of many, or maybe even the majority, of the cancer patients at the current time. Creative approaches are needed to increase access to genome-driven clinical trials, especially for patients with rare cancer types and for those treated outside of academic medical centres. To accelerate the development of novel drugs and drug targets, such efforts should be paired with genomic and clinical data sharing initiatives to provide sufficient power to define associations between specific genomic profiles and treatment response. Improved clinical decision support tools are also urgently needed to ensure that oncologists do not fail to recognize rare actionable variants, as well as

to discourage off-label use of speculative or inappropriate therapies that may expose patients to potential harm. Finally, accurate assessment of pre-existent tumour heterogeneity and detection of clonal evolution under the selective pressure of drug therapy will require the development of novel profiling methods, such as those using cell-free DNA input. However, the data unequivocally demonstrate that a meaningful minority of patients derive clinically important and sometimes dramatic benefit from genome-driven oncology, and we believe that a universal approach to NGS-based tumour profiling is now warranted.

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